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10/526,741	11/14/2005	Hiroyuki Aburatani	392.1001	4248

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EXAMINER	
REDDIG, PETER J	

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1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,741	ABURATANI ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02/24/2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9 and 25-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 25-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/15/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed February 24, 2010 in response to the Office Action of July 24, 1996 is acknowledged and has been entered. Previously pending claims 23 and 24 have been cancelled, claim 9 has been amended and new claims 30-41 have been added. Claims 9 and 25-41 are currently being examined.

Rejections Maintained

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 9 and 25-29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lage et al. (Virchows Arch 2001 438:567-573, IDS), in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85: 4852-4856), further in view of Dillman et al.(Annals of Internal Medicine 1989, 111:592-603), further in view of Mast et al. (Biochem. J. 1997, 327: 577-583), and further in view of Midorikawa (Proc. Amer. Assoc. Can. Res. March 2002, 43:11 Abstract #53). for the reasons previously set forth in the Office Action of July 9, 2008, section 2-pages 3-5, which are set forth below.

Lage et al. teach the production of a monoclonal antibody to GPC3 using an oligopeptide of amino acids 537-556 of human GPC3, see Materials and Methods. Lage et al. use the standard art technique of fusing spleen cells from immunized mice with myeloma cells to generate hybridomas for the production of the monoclonal antibody, which leads to recombination of the fused cellular genomes, thus the monoclonal antibodies are recombinant antibodies. Lage et al. teach that the glycosyl-phosphatidylinositol anchor GPC3 protein is expressed in hepatocellular carcinomas, decreasing in expression in tumor grade, see Abstract, table 1, Fig. 2-4.

Lage et al. does not teach that the antibody has any cytotoxic activity in vitro against the cell line HepG2 in the presence of complement or peripheral blood mononuclear cells or a humanized form of the antibody.

Steplewski et al. teach that mouse monoclonal antibodies are humanized to overcome the problem of short half-life and immunogenicity of murine monoclonal antibodies in humans, see page 4852, first paragraph. Steplewski et al. teach the generation of humanized mouse monoclonal anti-bodies using Cγ1, Cγ2, Cγ3, and Cγ4 human heavy chains and human Cκ light chains, see Materials and Methods. Steplewski et al. that these humanized antibodies can mediate antibody dependent cell mediated cytotoxicity, ADCC, *in vitro* in the presence of peripheral blood monocytes, see Abstract, Materials and Methods, and Fig.4.

Dillman teaches that IgG1, IgG2, IgG3, and IgG4 humanized mouse monoclonal antibodies mediate complement mediated cytotoxicity, see p. 593, 1st col.

Mast et al. teach that GPC3 is expressed on the surface of HepG2 cells, see Title, Abstract, and Introduction.

Midorikawa et al. teach that GPC3 protein is found in elevated levels in HepG2 cells and 22 of 52 hepatocellular carcinomas examined.

It would be *prima facie* obvious to one of skill in the art at the time the invention was made to humanize the monoclonal antibody of Lage et al. using the methods of Steplewski et al.

to make humanized monoclonal antibodies that have Cγ1, Cγ2, Cγ3, or Cγ4 human heavy chains and human Cκ light chains that have cytotoxic activity in the presence of complement or peripheral blood mononuclear cell as Steplewski et al. teach that humanization of antibodies is done to overcome the problems of using mouse monoclonal antibodies in human therapy. Additional Steplewski et al. teach that these humanized antibodies have cytotoxic activity toward cells expressing the target antigen in the presence of peripheral blood monocytes and Dillman teaches that IgG1, IgG2, IgG3, and IgG4 humanized mouse monoclonal antibodies mediate complement mediated cytotoxicity. One would have been motivated to humanize antibodies the monoclonal antibody of Lage et al. to screen them for potential therapeutic antibodies using HepG2 cells that expressed GPC3 on their surface given that Lage et al. and Midorikawa et al. teach that GPC3 is expressed in hepatocellular carcinomas, given that HepG2 cells express GPC3 on their cell surface at elevated levels, and given the importance of developing new cancer therapeutics. One of skill in the art would have had a reasonable expectation of success of making a humanized, monoclonal antibody against a peptide consisting of amino acid residues 375-580 of GPC/SEQ ID NO: 4 that has cytotoxic activity in vitro against HepG2 cells in the presence of mononuclear cells or complement given that the monoclonal antibody of Lage et al. binds within amino acid residues 375-580 of GPC3, the methods for humanizing antibodies were well known in the art at the time the invention was made, and the humanized antibodies claimed were known to have to cytotoxic activity in the presence of complement or peripheral blood mononuclear cells.

Applicants argue that in the Office Action, the Examiner alleges *inter alia* that a person skilled in the art at the time the invention was made would have humanized the monoclonal antibody of Lage et al. using the methods of Steplewski et al., in order to overcome the problems involved in using mouse monoclonal antibodies in human therapy.

Applicants argue that in addition, the Examiner alleges that Steplewski et al. teach that humanized antibodies have cytotoxic activity toward cells expressing the target antigen in the presence of peripheral blood monocytes, and Dillman et al. teach that humanized antibodies exhibit complement- mediated cytotoxicity. Thus, one would have been motivated to humanize the monoclonal antibody disclosed in Lage et al., given that GPC3 is highly expressed in HCC, given that HepG2 cells express GPC3 on their cell surface at elevated levels, and given the importance of developing new cancer therapeutics.

Applicants argue that the mouse antibody CQ 17-1A with a humanized modification originally has a high binding activity toward U-937 cells (see Steplewski et al., page 4853, left column, 5th paragraph "Binding of Chimeric mAbs to FcR" and Fig. 1). Applicants argue that on the contrary, the Be-F4 antibody of Lage et al. binds more tightly to the normal liver tissue than to hepatic cancer cells. One could never have been motivated to obtain a humanized antibody having desired properties to meet the goal of developing a new cancer therapy with a reasonable expectation of success by effecting humanized modification starting from the Be-F4 antibody having such a binding property.

Applicants argue that however, in order to expedite the prosecution of the present application, independent claim 9 of the present application has been amended without prejudice to add the feature of the antibody of the present invention "which is not expressed in normal liver." Applicants respectfully submit that the amended claims of the present invention further distinguish the present invention from the Be-F4 antibody disclosed in Lage et al.

Applicants argue that "An antibody against a peptide consisting of amino acid residues 375-580 of GPC3 as set forth in SEQ ID NO: 4 which is not expressed in normal liver" of the present invention as claimed in the amended Claim 9 is not disclosed nor suggested in Lage et al. The antibody of the present invention and the Be-F4 antibody disclosed in Lage et al. show opposite binding properties. Namely, the former is an antibody against the peptide 375-580 of GPC3 which is not expressed in normal liver tissue, and the latter binds more tightly to normal liver tissue than liver cancer cells. A person skilled in the art would have never been motivated to combine Lage et al. with Steplewski et al., further with Dillman et al., further with Mast et al., and further with Midorikawa et al. Also a person skilled in the art would have never had a

reasonable expectation of success in arriving at the present invention as claimed in Claim 9 which has an opposite binding property from the antibody Be-F4 which binds more tightly to normal liver tissue than hepatic cancer cells.

Applicants argue that in addition, the disclosure of Dillman et al. merely provides a general guidance of humanized antibodies but fails to provide a clear teaching or implication to direct someone toward the feature of the present invention. Mast et al. and Midorikawa et al. do not provide clear teaching or implication about the feature of the present invention "antibody against a peptide consisting of amino acid residues 375-580 of GPC3 as set forth in SEO ID NO:4" as recited in claim 9 of the present invention.

Applicants argue that accordingly, a person skilled in the art would have never had a reasonable expectation of success to achieve the present invention as claimed in Claim 9 which has an opposite binding property from the antibody Be-F4 which binds more tightly to normal liver tissue than hepatic cancer cells. In conclusion, a person skilled in the art could not have conceived of the present invention based on the combination of the cited references.

Applicants argue that the rejection of claims 23 and 24 is now moot as claims 23 and 24 have been cancelled without prejudice in the present paper. Claims 25 to 29 depend directly either directly or indirectly from independent claim 9 which is discussed above.

Applicants' arguments have been considered, but have not been found persuasive. First, there is no evidence that the antibody of Lage et al. differentially binds to GPC3 from different sources, e.g. normal or tumor tissue. Rather, the difference is in expression levels of GPC3, not the binding affinity of the antibody to GPC3 from different sources. See Fig. 3 and 4. Furthermore, there no evidence of record that the claimed GPC 3 peptide would be structurally

distinct whether it is expressed in normal liver, tumor tissue, or elsewhere. Thus, given that the antibody of Lage et al. was generated to an oligopeptide of amino acids 537-556 of human GPC3, it (or other antibodies to this peptide) or humanized forms thereof would bind and be against residues 357-580 of SEQ ID NO: 4, whether or not the GPC3 protein is expressed in normal liver. Thus, the antibody of Lage et al. would not have an opposite or distinct binding property and would bind the claimed GPC3 peptide. Thus given the combined teachings of Lage and Midorikawa, which both teach that GPC3 is expressed in hepatocellular carcinoma, and given that Mast et al. teach that GPC 3 is expressed on the cell surface of HepG2 cells, one of skill in the art would have been motivated with a reasonable expectatin of success of making recombinant humanized monoclonal antibodies that have CDC or ADCC activity in vitro against the cell line HepG2 in the presence of complement or peripheral blood mononuclear cells in view of Steplewski and Dillman who teach how to make humanized monoclonal antibodies that have ADCC or CDC activity in the presence of complement or peripheral blood mononuclear cells.

3. Claims 9 and 25-29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Filmus et al. (US Pat App. Pub. 2005/0233392 A1 May 23, 2002), in view of Steplewski et al. (Proc. Natl. Acad. Sci. USA, 1988 85: 4852-4856), further in view of Dillman et al. (Annals of Internal Medicine 1989, 111:592-603), further in view of Mast et al. (Biochem. J. 1997, 327: 577-583), and further in view of Midorikawa (Proc. Amer. Assoc. Can. Res. March 2002, 43:11 Abstract #53) for the reasons previously set forth in the Office Action of July 9, 20008, section 3-pages 5-7, which are set forth below.

Filmus et al. teach the production of a monoclonal antibody to GPC3 using the last 70 amino acids of human GPC3, see para 0098 and 0107-0109 and claims 7 and 33. Filmus et al.

use the standard art technique of fusing spleen cells from immunized mice with myeloma cells to generate hybridomas for the production of the monoclonal antibody, which leads to recombination of the fused cellular genomes, thus the monoclonal antibodies are recombinant antibodies, see para 0098 and 0107-0109. Filmus et al. teach that the monoclonal antibody 1G12 bound strongly to human liver tumor cells, but not normal hepatocytes, see Examples 4 and 5.

Filmus et al does not teach that the antibody has any cytotoxic activity in *vitro* against the cell line HepG2 in the presence of complement or peripheral blood mononuclear cells or a humanized form of the antibody.

Steplewski et al. teach that mouse monoclonal antibodies are humanized to overcome the problem of short half-life and immunogenicity of murine monoclonal antibodies in humans, see page 4852, first paragraph. Steplewski et al. teach the generation of humanized mouse monoclonal anti-bodies using Cγ1, Cγ2, Cγ3, and Cγ4 human heavy chains and human Cκ light chains, see Materials and Methods. Steplewski et al. that these humanized antibodies can mediate antibody dependent cell mediated cytotoxicity, ADCC, *in vitro* in the presence of peripheral blood monocytes, see Abstract, Materials and Methods, and Fig.4.

Dillman teaches that IgG1, IgG2, IgG3, and IgG4 humanized mouse monoclonal antibodies mediate complement mediated cytotoxicity, see p. 593, 1st col.

Mast et al. teach that GPC3 is expressed on the surface of HepG2 cells, see Title, Abstract, and Introduction.

Midorikawa et al. teach that GPC3 protein is found in elevated levels in HepG2 cells and 22 of 52 hepatocellular carcinomas examined.

It would be *prima facie* obvious to one of skill in the art at the time the invention was made to humanize the monoclonal antibody of Filmus et al using the methods of Steplewski et al. to make humanized monoclonal antibodies that have Cγ1, Cγ2, Cγ3, or Cγ4 human heavy chains and human Cκ light chains that have cytotoxic activity in the presence of complement or peripheral blood mononuclear cell as Steplewski et al. teach that humanization of antibodies is done to overcome the problems of using mouse monoclonal antibodies in human therapy. Additional Steplewski et al. teach that these humanized antibodies have cytotoxic activity toward cells expressing the target antigen in the presence of peripheral blood monocytes and Dillman teaches that IgG1, IgG2, IgG3, and IgG4 humanized mouse monoclonal antibodies mediate complement mediated cytotoxicity. One would have been motivated to humanize antibodies the monoclonal antibody of Filmus et al to screen them for potential therapeutic antibodies using HepG2 cells that expressed GPC3 on their surface at elevated levels given that Filmus et al. and Midorikawa et al. teach that GPC3 is expressed in hepatocellular carcinomas and given the importance of developing new cancer therapeutics. One of skill in the art would have had a reasonable expectation of success of making a humanized, monoclonal antibody against a peptide consisting of amino acid residues 375-580 of GPC/SEQ ID NO: 4 that has cytotoxic activity in vitro against HepG2 cells in the presence of mononuclear cells or complement given that the monoclonal antibody of Filmus et al binds within amino acid residues 375-580 of GPC3, the methods for humanizing antibodies were well known in the art at the time the invention was made, and the humanized antibodies claimed were known to have to cytotoxic activity in the presence of complement or peripheral blood mononuclear cells.

Applicants argue that in the Office Action, the Examiner alleges *inter alia* that a person skilled in the art at the time the invention was made would have humanized the monoclonal antibody 1 G12 disclosed in Filmus et al. using the methods of Steplewski et al, in order to overcome the problems involved in using mouse monoclonal antibodies in human therapy.

Applicants argue that in addition, the Examiner alleges inter alia that Steplewski et al. teach that humanized antibodies have cytotoxic activity toward cells expressing the target antigen in the presence of peripheral blood monocytes, and Dillman et al. teach that humanized antibodies exhibit complement-mediated cytotoxicity. Thus, one would have been motivated to humanize the monoclonal antibody disclosed in Filmus et al., given that GPC3 is highly expressed in HCC, given that HepG2 cells express GPC3 on their cell surface at elevated levels, and given the importance of developing new cancer therapeutics.

Applicants argue that the Examiner mentioned in the office action that the claims are not drawn to antibodies with inherent cytotoxic activity (page 9, line 17). Although the Applicants do agree with the Examiner's position, the Applicants have amended Claim 9 without prejudice to add the feature "having ADCC or CDC activity", in order to accelerate the examination.

Applicants argue that as they asserted in the response to the previous office action, it was well known in the art that the IG12 antibody disclosed in Filmus et al. did not exhibit cytotoxicity (e.g., ADCC activity and CDC activity) in unconjugated form. Accordingly, a person skilled in the art would never had a reasonable expectation of success in obtaining an antibody with ADCC activity or CDC activity as defined in the amended Claim 9 based on the 1 G12 antibody disclosed in Filmus et al. which clearly does not exhibit ADCC activity or CDC

activity, even in view of Steplewski et al, further in view of Dillman et al., further in view of Mast et al. and Midorikawa et al.

Applicants argue that in conclusion, a person skilled in the art could not have conceived of the present invention based on the combination of the cited references.

Applicants argue that the rejection of claims 23 and 24 is now moot as claims 23 and 24 have been cancelled without prejudice in the present paper. Claims 25 to 29 depend directly either directly or indirectly from independent claim 9 which is discussed above.

Applicants arguments have been considered, but have not been found persuasive. Althougt the monoclonal antibodies of Filmus et al. do not have ADCC or CDC by themselves, it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. *In re Young*, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); *In re Keller* 642 F.2d 413,208 USPQ 871 (CCPA 1981). In particular the combined references teach that it would be obvious to humanize the antibody of Filmus et al. and thus humanized versions of the Filmus et al. monoclonal antibodies with complement or mononuclear cell reactive Fc domains would be expected to have CDC or ADCC activity towards HepG2 cells in the presence of complement or peripheral blood mononuclear cells for the reasons previously set forth. Thus, given that both Filmus et al. and Midorikawa teach that GPC3 is expressed in hepatocellular carcinoma and given that Mast et al. teach that GPC 3 is expressed on the cell surface of HepG2 cells, one of skill in the art would have been motivated with a reasonable

expectatin of success of making recombinant humanized monoclonal antibodies that have CDC or ADCC activity in vitro against the cell line HepG2 in the presence of complement or peripheral blood mononuclear cells in view of Steplewski and Dillman who teach how to make humanized monoclonal antibodies that have ADCC or CDC activity in the presence of complement or peripheral blood mononuclear cells. As set forth, above the antibodies would be expected to bind withing residues 375-380 of SEQ ID NO: 4 regardless where the peptide is expressed because no evidence has been presented that the source of the proetin would affect antibody binding to this region.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 9 and 25-29 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 3, 6, 7, 16, 21, 22, 29, 32,

34, 38, 39, 41, 43-50 of copending Application No. 10/583,795, for the reasons set forth in section 4 of the Office Action of 09/01/2009, which are set forth below.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the isolated recombinant, humanized monoclonal antibodies with a human kappa constant chain and a human gamma-1 H chain constant region claimed in claims 3, 6, 7, 16, 21, 22, 29, 32, 34, 38, 39, 41, 43-50 of copending Application No. 10/583,795 bind to epitope bind to epitopes in amino acids 375-580 of GPC3/SEQ ID NO:4 and have ADCC and CDC activity against HepG2 cells in vitro, and thus are a species of the claimed instantly claimed cytotoxic monoclonal antibodies. See Table on pages 21-24 Examples 6, 13-29, and Figs. 8, 12, 19 and 20.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants acknowledge the rejection and submit that filing of a terminal disclaimer will be considered upon indication that the current claims or the pending claims of U.S. Patent Application No. 10/583,795 are otherwise allowable.

In response, given that no terminal disclaimer has been filed, the rejection is maintained for the reasons previously set forth.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 9 and 25-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The limitations of "a peptide consisting of amino acid residues 375-580 of GPC3 as set forth in SEQ ID NO:4 *which is not expressed in normal liver*", "The antibody in claim 9 comprising the CDR1, CDR2 and CDR3 of the H chain variable region as set forth in SEQ ID NO: 10 and the CDR1, CDR2 and CDR3 of the L chain variable region as set forth in SEQ ID NO: 18", and "The antibody in claim 9 comprising the CDR1, CDR2 and CDR3 of the H chain variable region as set forth in SEQ ID NO: 12 and the CDR1, CDR2 and CDR3 of the L chain variable region as set forth in SEQ ID NO: 20" claims in claims 9 and 25-41 do not have clear support in the specification and the claims as originally filed.

Applicants argue that support for the aforementioned amendment to claim 9 can be found in pages 42-43 of the specification as filed under the subtitle of "Expression Analysis of human GPC3 mRNA using GeneChip.

A review of the cited support shows support for a low level of GPC mRNA in normal liver and higher level expression of the mRNA in hepatoma. However, this does provide support for the a peptide consisting of amino acid residues 375-580 of GPC3 as set forth in SEQ ID NO:4 which is not expressed in normal liver, because there is expression of the GPC3 mRNA in normal liver, which would indicate expression of the protein in normal liver, in other words, the protein is expressed in normal liver. See Fig. 1.

Applicants argue that support for new claims 30 to 41 can be found in the present specification as filed, for example, from page 16, line 1 to page 20, line 20, and Example 4, as well as in the sequence listing

A review of the cited support reveals support for making monoclonal antibodies, making recombinant antibodies, chimeric antibodies with the V region fused to the C region of a human

antibody, humanized antibodies with the CDRs of non-human mammals, SEQ ID NO: 10, 12, 18 and 20, and chimeric forms of the monoclonal antibodies M3C11 and M1E07. This supports humanized antibodies and chimeric antibodies comprising the CDR1, CDR2 and CDR3 of the H chain variable region as set forth in SEQ ID NO: 10 and the CDR1, CDR2 and CDR3 of the L chain variable region as set forth in SEQ ID NO: 1 or humanized antibodies and chimeric antibodies comprising the CDR1, CDR2 and CDR3 of the H chain variable region as set forth in SEQ ID NO: 12 and the CDR1, CDR2 and CDR3 of the L chain variable region as set forth in SEQ ID NO: 20. However, it does support the broadly claimed antibodies of claim 30 and 36 which encompasses a broader genus of any type of antibody according to claim 9 comprising the recited CDRs. Furthermore, with regard to claims 33 and 39, the variable region comprising the CDRs of SEQ ID NOs: 10/18 and 12/20 are from mice not just any mammal. See Example 2 and 4.

Thus, the subject matter claimed in the amended and/or new claims 9 and 25-41 broadens the scope of the invention as originally disclosed in the specification.

6. All other objections and rejections recited of the Office Action of 09/01/2009 are withdrawn.

7. No claims allowed.

8. Applicant's amendment necessitated the new grounds of rejection. Thus **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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